### Introduction

Astronauts embarking on missions beyond low Earth orbit (LEO) will be exposed to a radiation field that may increase the risks of developing cancer, cardiovascular diseases, central nervous system disorders, and immune decrements. Operational parameters will be the primary determinants of crew radiation exposure. NASA uses integrated design tools and risk models to optimize these parameters to minimize radiation exposure. NASA is also considering medical countermeasures (MCMs) to reduce radiation-associated health risks. MCMs for potential use in space-based applications can be developed from a variety of sources, including:

- Population-based chemoprevention trials against targeted diseases
- Drug development efforts focused on treating acute effects from accidental radiation exposures
- Mechanistic studies of distinct damage caused by high charge (Z) particles
- Repurposing of agents developed for other applications
- Drug development to mitigate side effects of radiotherapy
- Accidental radiation exposures

Use of agents developed for other applications, or repurposed, is advantageous because long-term safety in humans is already established.

### Space Radiation Health Risks

**Unique Challenges**
- Radiation Quality Effects
- Low Dose-Rates in Space
- Understanding Individual Susceptibility
- Quantifying Combined Stressors – "Spaceflight Exposome"

DNA Damage in Cells: Space radiation (HZE) produces densely ionizing particle tracks associated with complex DNA damage and unique biological responses. ([Cucinotta & Saganti (left), Patel & Huff (right), NASA](https://www.nasa.gov/mission_pages/crewhealth/radiationhealth.html))

### Radiation Mitigation

**SR Drug Repurposing Pipeline - Example**

**D**-Gate - Agent Selection & Testing
- Identify Candidate Agents – literature review, pilot data, collaborators
- Agent worksheet with proposed testing schema and translational signature identified
- Advisor Panel Review
- Program Support

**P**ipeline for Space Radiation MCMs
- 20 - High throughput
- 3D-organoid - premalignant biology (es. inflammatory signature, genetic instability)
- "Fast" tumor models – (GEMMs, imaging for early tumor detection)
- Tumor models - GCR sim
- Tumor models – GCR sim, Alternate models, diversity outbred pop
- Astronaut avatar models / Digital twins
- Individual susceptibility, tailored treatment options

Decision-gate process for selection and testing of MCM for space radiation health risks.
- Increase likelihood of success by implementing defined criteria and protocols
- Candidate agent selection – must meet mission criteria, safety profiles, with supporting literature
- Testing protocol has a clearly established translational path
- Modeled after process developed by the National Cancer Institute (NCI) and Perlmutter Cancer Center (TAG-NCI)

**Testing**
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### Mitigation Strategies for Space Radiation Health Risks

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**Mission Specific Radiation Dose Estimates**
- Solar Cycle Location Duration Vehicle Shielding
- ISS Low Earth Orbit Magnetospheric protection 6 mo. 50-100 mld
- Furry and Mars Surface 2-3 yr missions Long deep space transit times
- Furry, Opposition/Stay & Conjunctions Long stay missions exposure estimates of 10-100 mld
- Mars missions are about three times to four times over PELs

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**Risk Reduction Strategies**
- **Pre-Mission**
  - Space Radiation Environmental Models and Mission Design (multi-)
  - "Evolving Models of Risk Projection": increases in dose with space missions (e.g., ISS, NASA)
  - Crew radiation, age and sex related effects
  - Improving for Individual Radiation Sensibility early disease indicators/gene variants
  - Enable longer mission durations
  - Allows for larger portion of crew office to quality of flight

- **In-Mission**
  - Mission Location & Duration
  - Solar Conditions: No to P
  - Optimal GCR shielding with respect to solar cycle
  - Operational Planning: Minimize exposure
  - Radiation/Health monitoring
  - Medical countermeasures: "radiation resilience decreases with radiation dose"
  - Biometric/Health monitoring: for early disease detection and health countermeasures
  - Radiation in Total Risk Profile
  - Increased quality of life & outcomes

- **Post-Mission**
  - Occupational Health Care for Astronauts
  - Advanced in Terminal and Post Mission: Prevention
  - Biomarkers: health monitoring for early disease detection and countermeasures
  - Medical countermeasures

### Summary

Radiation environment in space is associated with significant health risks to crew with development of late cancers as a key driver limiting safe days in space.

In addition to optimizing mission parameters and shielding to reduce space radiation exposure, development of effective medical countermeasures as a mitigation strategy, although challenging, is warranted. One approach is to use a streamlined decision-gate agent selection and testing process for agent evaluation modeled after process developed by the National Cancer Institute’s Division of Cancer Prevention.

- Leverage external body of evidence to screen drugs with known safety profiles – Repurposing
- Oversight by advisory panel to include flight surgeons, external experts, key NASA personnel
- Focus on chemoprevention – natural, synthetic, or biologic agents, able to delay, reverse, or inhibit tumor development
- Focus on highest risk tissues where early detection options are not robust, such as breast & lung, as well as cancers with short latency that have potential to manifest in-mission (leukemias)
- Leverage scientific knowledge and recent advances in understanding of premalignant biology
- Target agents with potential cross-risk efficacy
- Techno watch for advances in immunoprevention strategies, senolytic drugs, and precision medical approaches applicable to astronauts
- FDA animal rule approach will be used for agent validation, as required
- Partner with external agencies with common interests
- Develop risk assessment strategies incorporating MCM